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Comparative neurobiological effects of ibogaine and MK-801 in rats

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Abstract

Ibogaine is a plant-derived alkaloid with putative ‘anti-addictive’ properties. Although ibogaine binds to multiple targets in the brain, recent evidence suggests the drug acts as an *N*-methyl-D-aspartate (NMDA) antagonist similar to MK-801. The purpose of the present study was to compare neurochemical and neuroendocrine effects of ibogaine and MK-801 *in vivo*. Male rats received either *i.p.* saline, ibogaine (10 and 100 mg/kg), or MK-801 (0.1 and 1 mg/kg). Groups of rats ($N = 6$ –8/group) were decapitated 30 or 60 min after injection. Brains were harvested for analysis of dopamine (DA) and its metabolites, while trunk blood was collected for analysis of plasma corticosterone and prolactin. Ibogaine produced marked dose-dependent reductions in tissue DA with concurrent increases in the metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA). This profile of ibogaine-induced effects on DA metabolism was consistently observed in the cortex, striatum, olfactory tubercle, and hypothalamus. MK-801, on the other hand, did not reduce DA levels in any brain region but did cause modest region-specific elevations in DA metabolites. Ibogaine and MK-801 caused comparable elevations in circulating corticosterone, but only ibogaine increased prolactin. The present findings show that the effects of ibogaine on DA neurotransmission and neuroendocrine secretion are not fully mimicked by MK-801. Thus, the wide spectrum of *in vivo* actions of ibogaine can probably not be explained simply on the basis of antagonism at NMDA receptors. © 2000 Elsevier Science Ireland Ltd. All rights reserved.

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1. Introduction

Ibogaine is a plant-derived compound that has gained attention as a possible medication for treating substance use disorders (reviewed by Popik et al., 1995b). Evidence for the ‘anti-addictive’ properties of ibogaine has come from both preclinical and human studies. In rats, pretreatment with ibogaine decreases the self-administration of cocaine and morphine (Glick et al., 1991; Cappendijk and Dzoljic, 1993; Glick et al., 1994). The drug also alleviates withdrawal symptoms in morphine-dependent animals (Glick et al., 1992; Popik et al., 1995a; although see Sharpe and Jaffe, 1990). In a recent clinical investigation, Sheppard (1994) found

that a single ibogaine treatment completely prevented the appearance of withdrawal symptoms in opiate addicts. Collectively, such findings support the utility of ibogaine as a treatment for drug addiction.

Despite extensive research, the precise mechanism responsible for the anti-addictive properties of ibogaine is enigmatic. It is well established that the drug binds with low μ M potency to multiple neuronal targets in the brain including sigma-2 receptors (Bowen et al., 1995; Mach et al., 1995), serotonin (5-HT) and dopamine (DA) transporters (Mash et al., 1995a; Staley et al., 1996), μ and κ opioid receptors (Deecher et al., 1992; Pearl et al., 1995), and *N*-methyl-D-aspartate (NMDA) ion channels (Popik et al., 1994; Sweetnam et al., 1995). However, the role of these various binding sites in mediating specific actions of ibogaine has not been resolved. Biodistribution studies in rats show that

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brain levels of ibogaine range from 10 to 20 μM when measured 1 h after acute administration of 50 mg/kg, p.o. (Staley et al., 1996) or 40 mg/kg, i.p. (Hough et al., 1996). Thus the interaction of ibogaine with μM -affinity binding sites appears to be functionally relevant *in vivo*.

Recently some investigators have speculated that the anti-addictive properties of ibogaine might involve antagonist activity at NMDA-coupled ion channels, similar to the effects of MK-801 (Mash et al., 1995b; Popik et al., 1995a; Chen et al., 1996). This hypothesis has important implications since MK-801 is reported to block the long-term neuroadaptive changes associated with chronic administration of opioids, ethanol, and psychomotor stimulants (Karler et al., 1989; Trujillo and Akil, 1991; Wu et al., 1993). Ibogaine inhibits the binding of [^3H]MK-801 in brain membrane preparations (Popik et al., 1994; Sweetnam et al., 1995). Similar to MK-801, ibogaine blocks depolarizations evoked by NMDA in cultured hippocampal neurons and in intact motoneurons (Mash et al., 1995b; Popik et al., 1995a; Chen et al., 1996). Studies in mice show that ibogaine cross-generalizes to MK-801 as a discriminative stimulus and antagonizes NMDA-induced lethality (Popik et al., 1995a; Chen et al., 1996). Thus, ibogaine appears to exhibit MK-801-like properties in a variety of *in vitro* and *in vivo* assay systems.

With respect to the preceding discussion, it seems appropriate to further evaluate the NMDA antagonist properties of ibogaine. In the present work, we compared the acute effects of ibogaine and MK-801 on central DA metabolism and stress hormone secretion. We examined the actions of ibogaine and MK-801 on these particular neurobiological endpoints for several reasons. First, the essential role of DA neurons in mediating the addictive properties of abused drugs is well accepted (Wise and Bozarth, 1987; Koob and Bloom, 1988). Second, stress hormones, particularly hormones of the hypothalamic–pituitary–adrenal (HPA) axis, are known to modulate the acute and long-term effects of abused drugs (Piazza and Le Moal, 1996, 1997). It seems feasible therefore that the anti-addictive effects of ibogaine might involve changes in DA function and/or activity of the HPA axis. Finally, the effects of ibogaine on DA metabolism and neuroendocrine secretion have recently been studied, and this provides a convenient starting point for comparison to MK-801 (Ali et al., 1996; Baumann et al., 1997).

2. Methods

2.1. Animals

Adult male CD rats (250–350 g) from the National Center for Toxicological Research (NCTR) breeding colony were used in these studies. Animals were housed

two per cage under controlled conditions (lights on: 06:00–18:00 h) with free access to food and water. The housing facilities were fully accredited by the American Association of the Accreditation of Laboratory Animal Care, and experiments were carried out in accordance with Institutional Animal Care and Use Committee of the NCTR.

2.2. Experimental procedures

Rats received either i.p. saline, ibogaine (10 and 100 mg/kg), or MK-801 (0.1 and 1.0 mg/kg), and groups of rats ($N = 6$ –8/group) were subsequently decapitated 30 and 60 min later. Trunk blood was collected into heparinized tubes. Brains were removed from calvaria and dissected into frontal cortex, striatum, olfactory tubercle, and hypothalamus. Briefly, brains were placed ventral side up on an ice-cold stage where the olfactory tubercles were removed with microdissecting scissors. Coronal slices were made at the level of the optic chiasm and the mammillary bodies to yield three pieces of brain tissue (Glowinski and Iversen, 1966). The cortex and striatum were dissected from the fore-brain piece of tissue, whereas the hypothalamus was removed from base of the midbrain piece. The caudal piece, which included the cerebellum and brainstem, was discarded.

We have previously characterized the neurochemical and neuroendocrine effects of ibogaine given at 50 mg/kg, i.p. (Ali et al., 1996), so the 10- and 100-mg/kg doses used in the present study were chosen to provide important comparative information. These two doses of ibogaine represent: (1) a low dose which has been used as a training dose in drug discrimination studies (Schechter and Gordon, 1993); and (2) a high dose which causes dramatic tremors and ataxia (O'Hearn et al., 1993). The MK-801 doses were matched to the ibogaine doses based on pilot data from our laboratory, *in vitro* potency estimates, and reported *in vivo* behavioral effects (Hirimatsu et al., 1989; Popik et al., 1995a; Chen et al., 1996). Brain tissue and plasma samples were stored at -70°C until the time of assay.

2.3. Neurotransmitter determinations

Postmortem tissue levels of DA and its metabolites, 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), were determined by high-performance liquid chromatography coupled to electrochemical detection (HPLC-EC) as described by Ali et al. (1996). Briefly, brain tissue was weighed and added to a measured volume (20% W/V) of 0.2 N perchloric acid containing 100 ng/mg of the internal standard, 3,4-dihydroxybenzylamine (DHBA). The tissue was disrupted by ultrasonication, centrifuged (15 000 rpm for 7 min), and 150 μl of the supernatant

was filtered. Aliquots of 25 μ l were injected onto the HPLC-EC system for the separation of DA and its metabolites.

The analytical system included a Waters Model 510 HPLC pump (Milford, MA, USA), a Rheodyne Model 7125 injector (Cotati, CA, USA), a Supelco C-18 3 μ m reversed-phase analytical column (Bellefonte, PA, USA), and a Bioanalytical Systems LC-4B amperometric detector (W. Lafayette, IN, USA) equipped with a glassy carbon working electrode set at +750 mV relative to a Ag/AgCl reference. The mobile phase consisted of 70 mM potassium phosphate, 8% methanol, 1.02 mM 1-heptane sulfonic acid, at a final pH of 3.0. Chromatograms were recorded and integrated on a Perkin–Elmer LCI-100 integrator (Norwalk, CT, USA). The levels of DA, DOPAC, and HVA were calculated by comparing peak heights of unknowns to standards.

2.4. Plasma hormone determinations

Plasma corticosterone and prolactin concentrations were determined by double-antibody radioimmunoassay (RIA). Corticosterone was assayed using commercially available kits (ICN Biomedicals, Irvine, CA). Plasma samples (10 μ l) were analyzed in duplicate within a single assay, and the average intra-assay coefficient of variability was 7.5%. Prolactin was assayed using materials generously provided by the National Hormone and Pituitary Program (Baltimore, MD, USA). Antiserum directed against rat prolactin, rPRL-S-9, was diluted 1:437 500 and rPRL-RP-3 served as the reference standard. [125 I]Prolactin was obtained from Covance Laboratories (Vienna, VA, USA). Plasma samples (50 μ l) were analyzed in duplicate within a single assay, and the intra-assay coefficient of variability was 6.5%.

2.5. Statistical analysis

All neurochemical and hormone data were evaluated using analysis of variance (ANOVA) followed by Duncan's Multiple Range test for post hoc comparisons. A value of $P < 0.05$ was considered the minimum criterion for statistical significance.

Table 1
Post-mortem tissue levels of DA, DOPAC, and HVA in dissected brain regions from saline-treated control rats sacrificed at 30 and 60 min after injection

Brain region	30 min sacrifice (ng/g wet weight)			60 min sacrifice (ng/g wet weight)		
	DA	DOPAC	HVA	DA	DOPAC	HVA
Frontal cortex	51.4 $\pm$ 6.2	25.7 $\pm$ 2.5	12.9 $\pm$ 2.4	45.9 $\pm$ 5.8	22.8 $\pm$ 1.5	11.1 $\pm$ 0.8
Striatum	1315.2 $\pm$ 68.6	140.4 $\pm$ 8.8	78.8 $\pm$ 5.8	1368.9 $\pm$ 49.0	154.4 $\pm$ 5.6	88.0 $\pm$ 5.2
Olfactory tubercle	729.4 $\pm$ 27.5	99.7 $\pm$ 6.4	48.7 $\pm$ 3.5	713.5 $\pm$ 35.5	102.5 $\pm$ 3.5	44.6 $\pm$ 3.2

3. Results

3.1. Effects of ibogaine and MK-801 on DA metabolism

The control levels of DA, DOPAC, and HVA in the cortex, striatum, and olfactory tubercle (from saline-treated rats) are shown in Table 1. The effect of ibogaine on DA metabolism in these brain regions is illustrated in Fig. 1. For the sake of clarity, the data in Fig. 1 are expressed as a percentage of the control values shown in Table 1. DA was significantly decreased in all three regions when assessed 30 min after ibogaine injection: cortex ($F[2,17] = 4.51$, $P < 0.025$), striatum ($F[2,17] = 42.50$, $P < 0.00001$), and olfactory tubercle ($F[2,17] = 17.36$, $P < 0.0001$). Post hoc tests revealed the reduction in DA was significant at the 10- and 100-mg/kg doses in the cortex, but only at 100 mg/kg in the striatum and olfactory tubercle. DA levels were still reduced 60 min after ibogaine in the striatum ($F[2,17] = 20.99$, $P < 0.00001$) and olfactory tubercle ($F[2,17] = 15.89$, $P < 0.0001$), but not in the cortex. At the 60-min timepoint ibogaine-induced decreases in tissue DA were significant for 10 and 100 mg/kg. It is noteworthy that ibogaine caused a significant decrease in tissue DA in the hypothalamus at 30 min ($F[2,17] = 11.46$, $P < 0.001$) and 60 min ($F[2,17] = 13.3$, $P < 0.001$) after injection (data not shown).

DOPAC was increased by ibogaine at 30 min post-injection in the striatum ($F[2,17] = 39.11$, $P < 0.0001$) and olfactory tubercle ($F[2,17] = 6.47$, $P < 0.01$), but not in the cortex. The ibogaine-induced elevation of DOPAC was significant only at the 100-mg/kg dose, and this effect was sustained for at least 60 min in the striatum ($F[2,17] = 4.42$, $P < 0.025$). HVA was increased in striatum ($F[2,17] = 14.49$, $P < 0.001$) and olfactory tubercle ($F[2,17] = 7.58$, $P < 0.01$) 30 min after ibogaine injection, but this effect achieved significance only at the 100-mg/kg dose. HVA levels were augmented 60 min after ibogaine in all three brain regions.

Fig. 2 illustrates the effects of MK-801 on DA metabolism in the cortex, striatum, and olfactory tubercle. Similar to the data in Fig. 1, the results depicted in Fig. 2 are expressed as a percentage of control values shown in Table 1. MK-801 did not affect post-mortem

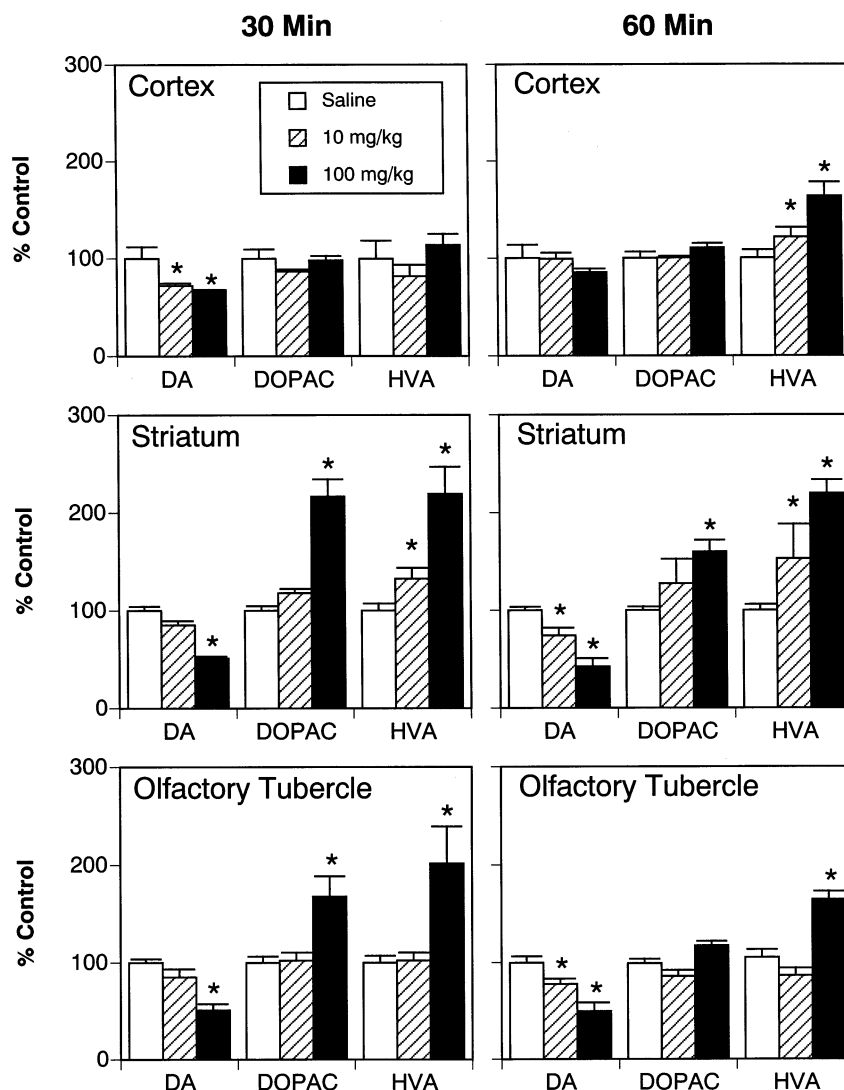


Fig. 1. Effect of i.p. saline or ibogaine (10 or 100 mg/kg) on DA, DOPAC, and HVA concentrations in the frontal cortex, striatum, and olfactory tubercle of male rats. Groups of rats ($N=6-8$ rats/group) were sacrificed 30 and 60 min after ibogaine treatment. Values are mean $\pm$ SEM expressed as % control of the data from saline-treated rats shown in Table 1. * $P < 0.05$ with respect to saline at a specific time point.

DA levels in the cortex, striatum or olfactory tubercle at either time point. Interestingly, MK-801 did cause an increase in hypothalamic DA at 30 min ($F[2,17] = 5.06$, $P < 0.01$) that was significant at both the 0.1- and 1.0-mg/kg doses (data not shown). DOPAC levels were increased 30 min after MK-801 in the striatum ($F[2,17] = 7.06$, $P < 0.01$) and olfactory tubercle ($F[2,17] = 23.23$, $P < 0.00001$), but not the cortex. Post hoc evaluation showed that the effect of MK-801 on DOPAC was statistically significant only at the 1.0-mg/kg dose of drug. The MK-801-induced elevation of DOPAC was maintained at 60 min in the olfactory tubercle ($F[2,17] = 16.76$, $P < 0.0001$). HVA levels were elevated 30 min after MK-801 in the striatum ($F[2,17] = 3.83$, $P < 0.05$) and olfactory tubercle ($F[2,17] = 6.63$, $P < 0.01$), and this effect was maintained at 60 min in the olfactory tubercle ($F[2,17] = 11.58$, $P < 0.001$).

3.2. Effects of IBO and MK-801 on stress hormones

Figs. 3 and 4 depict the effects of ibogaine and MK-801 on plasma hormone levels, respectively. As shown in Fig. 3, ibogaine elevated plasma prolactin when assessed at 30 min ($F[2,17] = 5.63$, $P < 0.01$) and 60 min ($F[2,17] = 6.02$, $P < 0.01$) post-injection. Both doses of ibogaine increased prolactin at 30 min, but only the 100-mg/kg dose caused persistent elevation of the hormone for 60 min. Corticosterone secretion was stimulated by ibogaine after 30 min ($F[2,17] = 30.50$, $P < 0.0001$) and 60 min ($F[2,17] = 113.88$, $P < 0.00001$). Post hoc analysis revealed that ibogaine-induced corticosterone secretion was significant only after the 100-mg/kg dose of drug. The data in Fig. 4 show that MK-801 had no effect on circulating prolactin levels. MK-801 was a potent stimulator of corticosterone secretion, with significant elevation of this hormone at 30

($F[2,17] = 32.71$, $P < 0.0001$) and 60 min ($F[2,17] = 63.14$, $P < 0.0001$) post-injection. The MK-801-induced increase in corticosterone was apparent at both 0.1 and 1.0 mg/kg doses.

4. Discussion

In the present study, acute ibogaine administration decreased brain tissue levels of DA along with concomitant increases in the DA metabolites, DOPAC and HVA. The drug also caused dose-related increases in plasma corticosterone and prolactin. It is noteworthy that ibogaine-induced reductions in brain DA and elevations in plasma prolactin were apparent after 10 mg/kg, i.p. (Figs. 1 and 3), a dose which is lower than

the typical anti-addictive dose of 40 mg/kg, i.p. (Glick et al., 1991, 1994). Moreover, the neurobiological effects of ibogaine reported herein are comparable to the results from previous studies that employed doses of ibogaine known to suppress cocaine and morphine self-administration in rats (Maisonneuve et al., 1992; Ali et al., 1996). Interestingly, the effects of MK-801 on these same neurobiological endpoints did not resemble the effects of ibogaine. For example, MK-801 failed to reduce tissue levels of DA in any brain region, even after a very high dose of 1.0 mg/kg. While MK-801 was a potent stimulator of corticosterone secretion, this drug did not affect prolactin. The collective results indicate that the effects of ibogaine on DA metabolism and prolactin secretion may not involve an MK-801-like action.

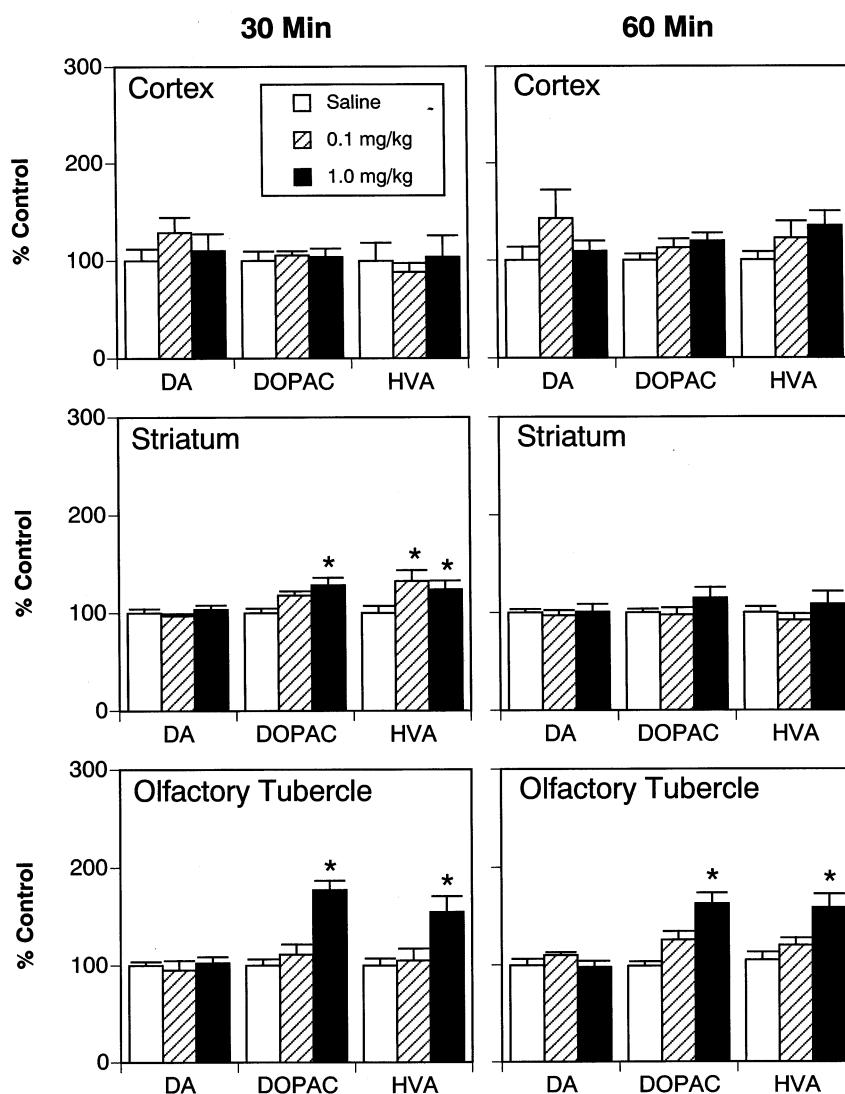


Fig. 2. Effect of i.p. saline or MK-801 (0.1 or 1.0 mg/kg) on DA, DOPAC, and HVA concentrations in the frontal cortex, striatum, and olfactory tubercle of male rats. Groups of rats ($N = 6-8$ rats/group) were sacrificed 30 and 60 min after MK-801 treatment. Values are mean $\pm$ SEM expressed as % control of the data from saline-treated rats shown in Table 1. * $P < 0.05$ with respect to saline at a specific time point.

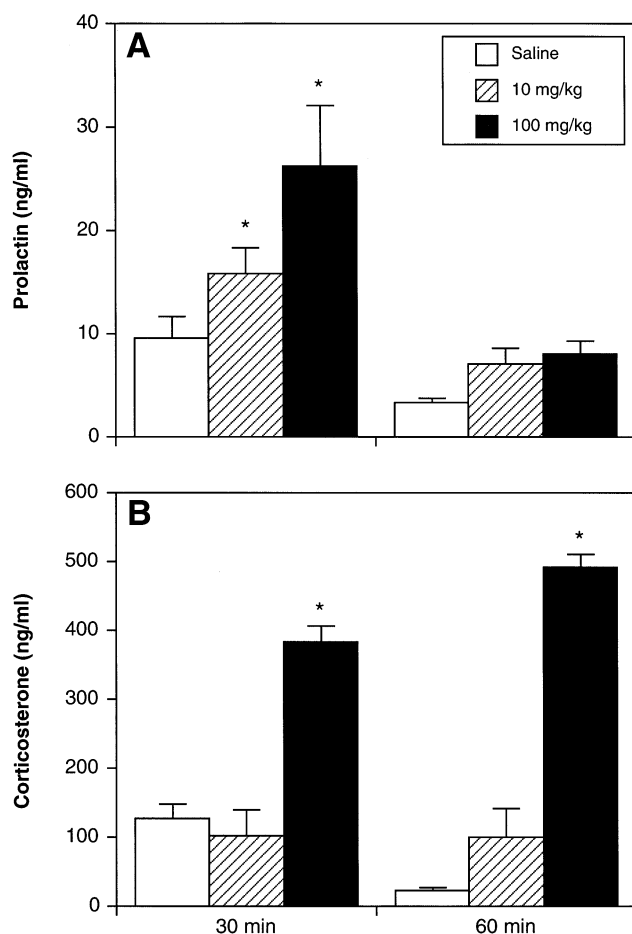


Fig. 3. Effect of i.p. saline or ibogaine (10 or 100 mg/kg) on plasma prolactin and corticosterone concentrations in male rats. Groups of rats ($N = 6-8$ rats/group) were sacrificed 30 min and 60 min after ibogaine treatment. Values are mean $\pm$ SEM expressed as ng/ml of plasma. * $P < 0.05$ with respect to saline at a specific time point.

As mentioned in the introduction, DA neurons are known to play a critical role in the locomotor stimulant and positive reinforcing properties of abused drugs (Wise and Bozarth, 1987; Koob and Bloom, 1988). Therefore, it seems conceivable that anti-addictive effects of ibogaine might involve alterations in central DA neurotransmission. Acute ibogaine caused dramatic reductions in tissue levels of DA along with a rise in the levels of DOPAC and HVA. This profile of ibogaine-induced effects was consistently observed in every brain region examined, and these results concur with previous studies performed in rats (Maisonneuve et al., 1992; Ali et al., 1996) and mice (Sershen et al., 1992). Interestingly, acute ibogaine pretreatment (40 mg/kg, i.p., –2 h) is reported to attenuate the cocaine-induced elevation in extracellular DA and its associated locomotor stimulation (Sershen et al., 1992; Broderick et al., 1994). In conjunction with the present data, such results suggest that ibogaine may diminish the effects of cocaine via a reduction in synaptic DA availability. On

the other hand, the effects of ibogaine observed in our study were acute (i.e. within 30–60 min) whereas some anti-addictive effects of the drug are long-lasting (> 19 h). Thus, our findings are not necessarily related to the persistent actions of ibogaine.

MK-801 did not mimic the effects of ibogaine on DA metabolism. Tissue levels of DA were never decreased by MK-801 even at high doses. In fact, MK-801 caused significant increases in hypothalamic DA (data not shown). Analogous to ibogaine, MK-801 significantly elevated DOPAC and HVA levels. In contrast to ibogaine, however, the effects of MK-801 on DA metabolites were region specific as reported by others (Hiraimatsu et al., 1989; Rao et al., 1990). Rao et al. (1990) used doses of MK-801 identical to our study (0.1 and 1.0 mg/kg) and showed that MK-801 increases DA metabolites, without altering DA levels, in striatum and olfactory tubercle. These data indicate that the acute actions of ibogaine on DA transmission probably do not involve blockade of NMDA-coupled ion channels.

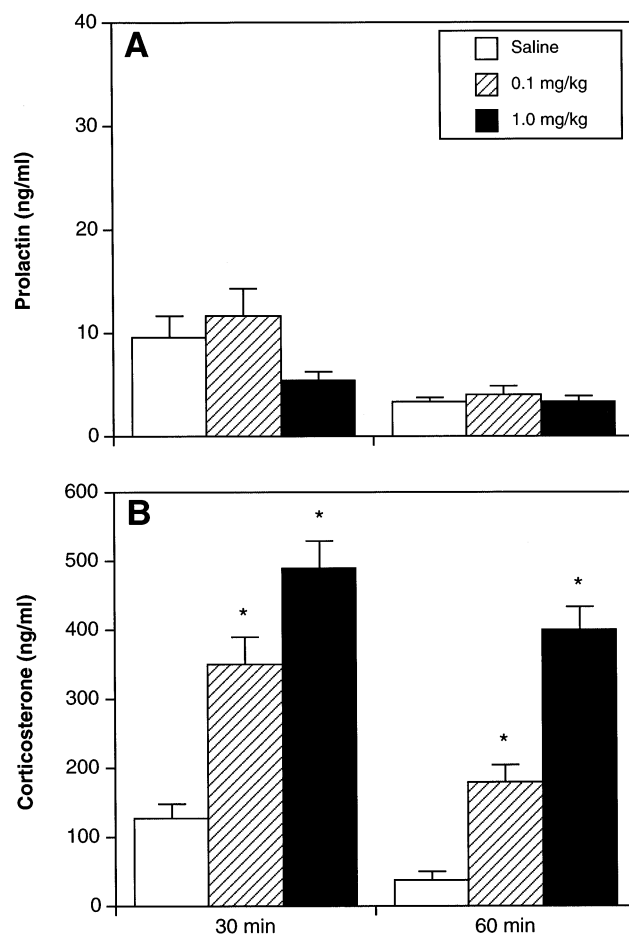


Fig. 4. Effect of i.p. saline or MK-801 (0.1 or 1.0 mg/kg) on plasma prolactin and corticosterone concentrations in male rats. Groups of rats ($N = 6-8$ rats/group) were sacrificed 30 and 60 min after MK-801 treatment. Values are mean $\pm$ SEM, expressed as ng/ml plasma. * $P < 0.05$ with respect to saline at a specific time point.

The mechanism(s) whereby ibogaine affects DA function is unclear. While ibogaine does not display significant affinity for DA receptors (Deecher et al., 1992; Sweetnam et al., 1995), the drug does bind with low μM potency at DA transporters labeled by the cocaine congeners [^3H]WIN-35,248 and [^{125}I]RTI-121 (Sershen et al., 1992; Mash et al., 1995a; Staley et al., 1996). On the other hand, Broderick et al. (1994) reported that ibogaine has greater than 100 μM affinity for DA transporters labeled with the piperazine derivative [^3H]GBR-12935. These apparently discordant findings might be explained by the findings of Vaughan (1995) who showed that cocaine congeners and GBR-analogs bind to different domains on DA transporters. Ibogaine appears to selectively interact with the high-affinity cocaine recognition site on the DA transporter. The precise nature of this interaction, however, remains to be determined.

In vivo microdialysis studies in rats demonstrate that ibogaine alters extracellular DA concentrations differentially, depending upon brain region. When examined 1 h after ibogaine injection (40 mg/kg, i.p.), dialysate DA is increased in the frontal cortex, decreased in striatum, and unaltered in the nucleus accumbens (Maisonneuve et al., 1991). More recent studies have confirmed that ibogaine does not affect extracellular DA in nucleus accumbens (Broderick et al., 1994; Mash et al., 1995a). The region specific effects of ibogaine on extracellular DA are distinct from the uniform effects of the drug on post-mortem indices of DA metabolism across brain areas. Taken together the data suggest that ibogaine may interact with DA transporter sites, but the effects of the drug on DA metabolism are not secondary to elevation of synaptic DA.

In a recent study, Staley et al. (1996) proposed that ibogaine might promote a 'reserpine-like' redistribution of intraneuronal DA from vesicular to cytoplasmic pools. While this hypothesis is purely speculative, there is evidence supporting the concept. Ibogaine displays low μM potency at vesicular monoamine transporters (VMAT) labeled with [^{125}I]tetraabenazine (Staley et al., 1996); these sites are crucial for the accumulation of DA into synaptic vesicles. An ibogaine-induced effect on VMAT, which disrupts compartmentalization of DA within vesicles, could redistribute DA into the cytoplasm. Under such circumstances, rapid metabolism of transmitter by monoamine oxidase would account for the dramatic decrease in tissue DA content and the parallel increase in acid metabolites.

Behavioral findings are consistent with the notion that ibogaine might impair vesicular storage of DA, at least transiently. Sershen et al. (1992) showed that acute ibogaine pretreatment (40 mg/kg, i.p., –2 h) blocks locomotor activity produced by cocaine, but not amphetamine, in mice. It is well established that cocaine-induced locomotor stimulant effects are dependent

upon a reserpine-sensitive vesicular pool of DA, whereas the effects of amphetamine are not (reviewed by McMillen, 1983). Thus ibogaine is reserpine-like in its ability to distinguish between two type of stimulants: DA reuptake blockers (i.e. cocaine) and DA releasers (i.e. amphetamine). Clearly, more studies examining the effects of ibogaine on DA neuronal dynamics are needed to address this proposed mechanism of action.

In the present work, ibogaine caused a transient rise in plasma prolactin and a prolonged increase in plasma corticosterone. MK-801 did not affect prolactin but did stimulate corticosterone secretion, confirming the findings of Pechnick et al. (1989). These investigators demonstrated that MK-801 causes parallel elevations of circulating adrenocorticotropin (ACTH) and corticosterone via a central mechanism (Pechnick et al., 1989). Thus, IBO-induced corticosterone secretion could be mediated by an MK-801-like action in the brain. Emerging evidence suggests that corticosterone is involved in the vulnerability to drug addiction and the acute reinforcing effects of abused drugs (Piazza and Le Moal, 1996, 1997). If this is indeed the case, the effects of ibogaine on corticosterone secretion might be involved in the anti-addictive effects of this drug. For instance, repeated injections of MK-801 result in tolerance to the drug-induced stimulation of the HPA axis (Pechnick et al., 1989). If ibogaine exposure likewise impairs the corticosterone-release mechanism, then this could reduce the reinforcing actions of subsequently self-administered drugs. Further experiments are necessary to examine the relationships between ibogaine, NMDA-coupled ion channels, and corticosterone secretion.

The mechanism(s) underlying the prolactin-releasing capability of ibogaine is not known. Preliminary data indicate this effect is centrally-mediated since intraventricular administration of ibogaine (50–200 μg) increases circulating prolactin in rats (Baumann, unpublished). It is logical to assume that DA is involved with the prolactin response to ibogaine because hypothalamic DA exerts a major inhibitory influence on the secretion of this hormone (Ben-Jonathan, 1985). If ibogaine decreases extracellular DA in the median eminence, as it does in the striatum, then prolactin secretion would be stimulated due to removal of DA inhibition. The ibogaine-induced decrease in tissue DA that we observed in the hypothalamus is consistent with this proposal, especially when viewed in the context of the reserpine-like effects of ibogaine mentioned previously.

In summary, ibogaine caused a spectrum of actions, which included stimulation of central DA metabolism and elevation of stress axis hormones. MK-801 did not fully mimic the effects of ibogaine on these specific response variables. On the other hand, a preponderance of evidence suggests ibogaine does mimic the effects of

MK-801 in a variety of in vitro and in vivo bioassay systems (Mash et al., 1995b; Popik et al., 1995a; Chen et al., 1996). The explanation for this apparent paradox could be related to the fact that NMDA-coupled ion channels represent only one of multiple ibogaine targets in the brain. In addition, MK-801 may bind to sites where ibogaine does not act. As pointed out by others, the non-selective nature of ibogaine may be the defining characteristic of the drug's therapeutic potential (Mash et al., 1995a; Sweetnam et al., 1995; Staley et al., 1996). Stated another way, the ability of ibogaine to simultaneously influence neural pathways involved with cognition (NMDA), mood (5-HT), and reward (DA), might underlie the unique anti-addictive effects of the drug. Future investigations should address the relative importance of specific ibogaine binding sites in mediating specific in vivo actions of ibogaine.

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